Case 1: Young woman with a mediastinal mass

- 23-year-old woman presents with dry non-productive cough with a recent history of 8 pounds of unexplained weight loss. She presents to the local UrgiCenter where a respiratory PCR was positive for metapneumovirus and she is managed conservatively. She has a worsening cough and 5 pounds of further weight loss. She returns and a CXR reveals a large mediastinal mass. She is referred to a pulmonologist and the mass is confirmed by CT of the chest with maximal diameter of 11 cm. Transbronchial FNA reveals large atypical cells with expression of CD30 “consistent with classical Hodgkin lymphoma”.
- She is referred to you. You recommend:
  1. Completion of pretreatment evaluation and ABVD + ISRT
  2. Completion of pretreatment evaluation and ABVD
  3. Completion of pretreatment evaluation and escBEACOPP
  4. Completion of pretreatment evaluation with mediastinoscopy
Case 1: Continued

- She undergoes mediastinoscopy and there are large cells with areas of sclerosis. The neoplastic cells EXPRESS CD20, OCT-2, BOB.1, CD30 (weak), CD23, TRAF-1 and c-REL and DO NOT EXPRESS CD10, CD15, MUM1/IRF4.
- The diagnosis is most consistent with:
  1. Diffuse large B-cell lymphoma, NOS
  2. Primary mediastinal large B-cell lymphoma
  3. Classical Hodgkin lymphoma, nodular sclerosing type
  4. Mediastinal grey zone lymphoma

Pathology of Primary Mediastinal Diffuse Large B-Cell Lymphoma (PMBL)
PMBL: Gene Expression Profiling Identifies Relationship Between PMBL and cHL


PMBL: Immunohistochemistry (IHC) Including Expression of PD-L2

- Markers distinguishing DLBCL v PMBL:
  - MAL; phosphorylated-STAT6; p63; TRAF5; activated (nuclear) cRel; TNFAIP2; CD23; CD200; PD-L2
- Abnormalities involving chromosome 9p24.1:
  - PMBL (70%); cHL (30%); DLBCL (rare)
- Potential key genes at 9p24.1:
  - PDCD1LG2, CD274, JAK2, and JMJ2DC
  - Amplification of 9p24.1 is often associated with increased transcription of all 4 genes
  - Gene expression profiling studies indicate relative overexpression of PD-L2 typically exceeds that of PD-L1 in PMBL

Min et al., Amer J Surg Path (2014), 38, 1715-1723;
Lenz et al., ASH annual meeting, 2007;
Mediastinal Grey Zone Lymphoma (MGZL): An entity between HL and PMBL with an inferior outcome

- **MGZL**
  - **Morphology**: May be more like cHL (~63%) or PMBL (~33%); some may appear composite (~4%)
  - **B-Cell**: CD20+ (strong ~70%); BCL6 (~85%)
  - **HL**: CD30 (100%); CD15 (~50%, variable)
  - **Infiltrating Dendritic Cells**: (measured by expression of dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin [DC-SIGN]) ~50%, variable.

![Image of MGZL staining](media/68b33b.png)

Outcome with DA-EPOCH R PMBL and MGZL

![Graphs showing EFS and OS](media/4c3f3c.png)


---

**Case 1: Continued**

- Your treatment recommendation for this patient is:
  1. R-CHOP
  2. R-CHOP + involved site radiation therapy
  3. DA-EPOCH-R
  4. Sequential R-CHOP/ICE

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**PMBL: Therapy**

**Dose-adjusted (DA)-EPOCH-R**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>375 mg/m² day 1 IVPB</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>10 mg/m²/day x 4 by CI</td>
</tr>
<tr>
<td>Vincristine</td>
<td>0.4 mg/m²/day x 4 by CI</td>
</tr>
<tr>
<td>Etoposide</td>
<td>50 mg/m²/day x 4 by CI</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>750 mg/m² day 5 IVPB</td>
</tr>
<tr>
<td>Prednisone</td>
<td>60 mg/m² BID days 1-5 oral</td>
</tr>
<tr>
<td>Filgrastim*</td>
<td>Weight-adjusted dose starting day 5 until ANC &gt; 5000/μL</td>
</tr>
</tbody>
</table>

*Recent data from MSKCC showed identical rate of dose-adjustment with filgrastim or pegfilgrastim*

- Dosed every 21 days if ANC > 1/μL and PLTS > 100K/μL
- Dose-adjusted based on ANC nadir:
  - >500/μL, increase cytotoxic drugs by 20%
  - <500/μL for 1-3 days, no change
  - <500/μL for >3 days or FN, decrease cytotoxic drugs by 20%

PMBL: DA-EPOCH-R Patient Characteristics

Table 1. Baseline Characteristics of the Study Patients.\(^*\)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Prospective NCI Cohort (N=53)</th>
<th>Retrospective Stanford Cohort (N=16)</th>
<th>P Value between Study Cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex — no. (%)</td>
<td>30 (59)</td>
<td>9 (56)</td>
<td>1.00</td>
</tr>
<tr>
<td>Age — yr</td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Median</td>
<td>30</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>19–52</td>
<td>21–68</td>
<td></td>
</tr>
<tr>
<td>Bulky tumor, ≥10 cm</td>
<td></td>
<td></td>
<td>0.57</td>
</tr>
<tr>
<td>Patients — no. (%)</td>
<td>33 (65)</td>
<td>9 (56)</td>
<td></td>
</tr>
<tr>
<td>Maximal diameter range — cm</td>
<td>5–18</td>
<td>7–18</td>
<td></td>
</tr>
<tr>
<td>Stage IV disease — no. (%)</td>
<td>15 (29)</td>
<td>7 (44)</td>
<td>0.36</td>
</tr>
<tr>
<td>Elevated lactate dehydrogenase level — no. (%)</td>
<td>40 (78)</td>
<td>11 (69)</td>
<td>0.51</td>
</tr>
<tr>
<td>Extramedul site — no. (%)</td>
<td>27 (53)</td>
<td>9 (56)</td>
<td>0.02</td>
</tr>
<tr>
<td>Pleural effusion — no. (%)</td>
<td>24 (47)</td>
<td>10 (62)</td>
<td>0.39</td>
</tr>
<tr>
<td>CD20+ malignant cells — no. (%)</td>
<td>51 (100)</td>
<td>16 (100)</td>
<td>1.00</td>
</tr>
<tr>
<td>BCL6+ malignant cells — no. (%)</td>
<td>33/17 (89)</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

\(^*\) BCL6 denotes the B-cell lymphoma 6 protein. NCI: National Cancer Institute, and ND not done.


PMBL: DA-EPOCH-R PFS and OS

PMBL: DA-EPOCH-R impact on cardiac ejection fraction


PMBL: FDG-PET-CT Findings after DA-EPOCH-R

<table>
<thead>
<tr>
<th>Lymphoma Status</th>
<th>Maximum Standardized Uptake Value</th>
<th>FDG-PET-CT Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤ Value in Mediastinal Blood Pool</td>
<td>&gt; Value in Mediastinal Blood Pool</td>
</tr>
<tr>
<td>(N=18)</td>
<td>total</td>
<td>value ≤5</td>
</tr>
<tr>
<td>No disease (no. of patients)</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Disease recurrence (no. of patients)</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

Sensitivity: 100%
Specificity: 54%
Positive predictive value: 17%
Negative predictive value: 100%


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**Sequential R-CHOP ⇒ ICE (MSKCC 01-142 and 08-026) PMBL Patients: Outcomes**

- **PMBL Overall Survival**
  - 70 pts: OS censored
  - Cumulative Survival
  - Time in Months

- **PMBL Progression Free Survival**
  - 70 pts: PT censored
  - Cumulative Survival
  - Time in Months

---

**MSKCC 01-142/08-146: DLBCL-Risk Adapted for Therapy**

- Prospective, biopsy controlled determination of "positive PET"
- Treatment is adapted by biopsy, not PET
- No radiation therapy permitted except for testicular disease
- IT methotrexate for aaHR, paranasal sinus, testis, BM
- Two studies with highly similar outcomes, combined analysis


---

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Sequential R-CHOP ➔ ICE (MSKCC 01-142 and 08-026) PMBL Patients: Interim FDG-PET


PMBL Principles

• More frequent in young women

• Important to avoid radiation therapy to minimize risk of breast cancer and late cardiovascular complications

• DA-EPOCH-R or sequential R-CHOP/ICE are reasonable options
  – No randomized trials are available

• Large scale trials have not been performed with either regimen

• Immune checkpoint inhibitors have a rationale in PMBL and need to be more fully evaluated
Case 2: Young man with a cervical mass

- 32-year-old man found a “lump in my neck when I was shaving a month ago”. He presented to his PCP who identified a 2.5 x 2 cm firm, non-tender left cervical mass. The mass did not resolve after a course of amoxicillin-clavulanate. He is referred for biopsy demonstrating diffuse effacement of the nodal architecture by large cells that EXPRESS CD20, CD10, MUM1/IRF4 and DO NOT EXPRESS CD5, BCL6. Ki-67 stains 70% of the large cells. The diagnosis is:
  1. DLBCL, germinal center
  2. DLBCL, non-germinal center
  3. PMBL
  4. Follicular lymphoma, grade 3B

Pathology of DLBCL
DLBCL, NOS and other Large B-cell Disorders: WHO 2008

- Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous group of disorders with varied natural history, genetic abnormalities, and response to therapy
- DLBCL, NOS: 31%
- Primary mediastinal (thymic) large B-cell lymphoma: 2%
- Variants: ~3%
  - T-cell/histiocyte rich large B-cell lymphoma
  - Primary cutaneous DLBCL, leg type
  - EBV positive DLBCL of the elderly
  - DLBCL associated with chronic inflammation
  - Lymphomatoid granulomatosis (EBV)
  - Intravascular large B-cell lymphoma
  - ALK positive large B-cell lymphoma
  - Primary CNS large B-cell lymphoma

Tumor Heterogeneity in DLBCL

DLBCL: Cell of Origin (COO) by Hans Model


Cell of Origin: Immunohistochemistry v GEP

- There are several models for determination of cell of origin (COO)
  - They lack precision but can be used to enrich populations for GC or non-GC
- RNA-based gene expression profiling (GEP) is a research tool, not useful in clinical practice
- Robust platforms that use formalin-fixed, paraffin-embedded tissue are need for COO determination
  - Hybrid capture/fluorescent reporter
  - Hybrid capture/S1 nuclease
  - Microfluidic PCR arrays

Performance of the Lymph2Cx assay in the independent validation cohort

Scott D W et al. Blood 2014;123:1214-1217

Patient outcomes according to COO in the independent validation cohort

Scott D W et al. Blood 2014;123:1214-1217
**Value of the Lymph2Cx assay**

- It is a robust 20-gene predictor of GCB vs ABC built for FFPE samples
- Accurately assigns cell-of-origin categories
- Inexpensive (< $40) and can be done in less than 36 hours
- It is highly reproducible between laboratories
- It retains prognostic power compared to fresh tissue-based GEP

Scott D W et al. Blood 2014;123:1214-1217

**Next Generation Sequencing of Commonly Mutated Genes: “FISH” for Genomics**

- Sequencing a limited number of genes is to whole genome sequence as FISH is to cytogenetics
- Sequencing limited number of genes allows for greater “depth” of sequencing
  - Whole genome sequencing has coverage of 10-50x
  - Hybrid capture on limited genes (300-600) has coverage of 300-500x
  - Permits identification of small clones within a population of tumor cells
Targeted Sequencing in DLBCL: “FISH” for Genomics

Case 2: Young man with a cervical mass

- Your treatment recommendation is:
  1. R-CHOP
  2. DA-EPOCH-R
  3. Sequential R-CHOP/ICE
  4. Clinical trial of lenalidomide and R-CHOP
Clinical Management

International Standard of Care: R-CHOP

Rituximab 375 mg/m² day 1
Cyclophosphamide 750 mg/m² day 1
Doxorubicin 50 mg/m² day 1
Vincristine 1.4 mg/m² day 1 (2 mg max)
Prednisone 40 mg/m² (or 100 mg) daily x 5

Age > 60
Pegfilgrastim 6 mg subcut day 2

Original Gela LNH 98-5 confirmed in multiple studies

Coiffier et al. ASCO 2007;Abstract 8009.
Is the dose of rituximab optimal? SEXIE-R-CHOP-14

RICOVER-60: Do difference in rituximab PK account for Male v Female outcome differences

Rituximab Trough Serum Levels

Older woman are the outliers

Pfreunschuh et al. ASCO 2014; Müller et al., Blood 2012, Pfreundschuh et al., Blood 2014
SEXIE-R-CHOP-14: Study Design and demographics

Pfreundschuh et al., Blood 2014

Equalizing rituximab exposure improves outcomes in men versus women >65

Pfreundschuh et al., J Clin Oncol 2014;32 (15_suppl):Abstract 8501.
Alternative anti-CD20 antibody: Obinutuzumab

Comparison of FDA-approved anti-CD20 antibodies

<table>
<thead>
<tr>
<th></th>
<th>Rituximab</th>
<th>Ofatumumab</th>
<th>Obinutuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>I</td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>+</td>
<td>-/+</td>
<td>++</td>
</tr>
<tr>
<td>ADCC</td>
<td>++</td>
<td>+/-</td>
<td>+++</td>
</tr>
<tr>
<td>Complement fixation</td>
<td>++</td>
<td>+++</td>
<td>+/-</td>
</tr>
</tbody>
</table>

GATHER (GAO4915g): Study design

Previously untreated DLBCL (n = 100)
Obinutuzumab: 1,000 mg d1, d8, d15, cycle 1; d1, cycles 2–8, every 21 days
CHOP: cyclophosphamide 750 mg/m² d1, doxorubicin 50 mg/m² d1, vincristine 1.4 mg/m² d1, prednisone 100 mg/day d1–5; cycles 1–6, every 21 days

Primary endpoint
• ORR (CR + PR)

Secondary endpoints
• PFS
• Response duration
• PK
• Pharmacodynamics
• Safety
• Biomarkers

Exploratory analyses
• Overall survival
• Prognostic value of FDG-PET
• FcγR polymorphism status

Evaluation
• Baseline and end of treatment FDG-PET scans, as well as CT scans after cycles 4 and 8 during study treatment
• FDG-PET scan will be performed after cycle 1 in the first 40 patients and after cycle 2 in the second 40 patients to explore its value in predicting patient outcomes
• Clinical tumour assessments will be performed every 3 months for 24 months, and then every 6 months for a further 12 months

Zelenetz et al, ASH 2013: Abstract 1820; manuscript in preparation

Obinutuzumab-CHOP (G-CHOP) for DLBCL, median follow up 28 months

All Patients

By Cell of Origin*

*Cell of origin determined by microfluidic PCR (microfluidic dynamic arrays) using a modified Wright classifier

Zelenetz et al, ASH 2013: Abstract 1820; manuscript in preparation
Alternatives to CHOP + anti-CD20 antibody

Infusional Therapy: DA-EPOCH-R
## Dose-Adjusted (DA)-EPOCH-R

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
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**Filgrastim***: Weight-adjusted dose starting day 5 until ANC > 5000/μL

*Recent data from MSKCC showed identical rate of dose-adjustment with filgrastim or pegfilgrastim

- Dosed every 21 days if ANC > 1/μL and PLTS > 100K/μL
- Dose-adjusted based on ANC nadir:
  - >500/μL, increase cytotoxic drugs by 20%
  - <500/μL for 1-3 days, no change
  - <500/μL for >3 days or FN, decrease cytotoxic drugs by 20%


## CALGB 59910: Multi-center DA-EPOCH-R, Outcomes

![Graphs A, B, C, D, E, F]

**CALGB 59910: Multi-center DA-EPOCH-R, Outcomes by biomarkers**

![Graphs showing outcomes by biomarkers](image)


---

**CALGB 50303: DA-EPOCH-R vs RCHOP21**

![Diagram showing randomization and outcomes](image)

- **OBJECTIVES:**
  - **Primary**
    - EPS untreated de novo DLBCL treated with RCHOP vs DA-R-EPOCH
    - Determine molecular predictors of outcome (using molecular profiling) in patients treated with these regimens.
  - **Secondary**
    - Compare ORR and OS
    - Compare the toxicity of these regimens in these patients.
    - Correlate the clinical parameters (i.e., toxicity, response, survival outcomes, and laboratory results) with molecular profiling in patients treated with these regimens.
    - Determine the use of molecular profiling for pathological diagnosis

- **FULLY ACCRUED, AWAITING EVENTS**
DLBCL: R-CHOP-21 or R-CHOP-14?

R-CHOP-14 v R-CHOP-21

- Three trials
  - GELA
    - Growth factor left to the discretion of the investigation
    - Dose intensity was poor on the R-CHOP-14 arm
    - No difference in PFS/OS
    - Toxicity favors R-CHOP-21
  - UK NCRI Lymphoma Clinical Study Group (CRUKE/03/019)
    - Growth factor as per the described regimens (R-CHOP-14 mandatory, R-CHOP-21 as clinically indicated
    - No difference in PFS/OS
    - Toxicity favors R-CHOP-14
  - DHLSG
    - Results not yet reported
Sequential Non-cross resistant chemotherapy

**MSKCC 01-142/08-146: DLBCL-Risk Adapted for Therapy**

- Prospective, biopsy controlled determination of "positive PET"
- Treatment is adapted by biopsy, not PET
- No radiation therapy permitted except for testicular disease
- IT methotrexate for aaHR, paranasal sinus, testis, BM
- Two studies with highly similar outcomes, combined analysis

Sequential R-CHOP x 4/ICE x3: Overall and Progression Free Survival


Prognostic factors

**LNH03-2B: R-ACVBP v R-CHOP**

Patients: Untreated DLBCL, age 18-59, aaIPI score =1 (high LDH, stage III/IV, ECOG PS >1)

*R-ACVBP 14*

- MTX
- R-IFM-VP16
- Ara-C

R

- 4 IT-MTX

*R-CHOP 21*

- 0 2 4 6 10 14 18 24 Wks

*No radiotherapy in both arms*


---

**LNH03-2B: Influence of Cell of Origin**

Hans score=GC

Hans score=n-GC

Benefit of the dose dense sequential R-ACVBP appears to be limited to non-GC patients

Molina T. et al ASH Annual Meeting 2011; Abstract 2632
## Comparison of R-CHOP/ICE and ACVBP with Consolidation

<table>
<thead>
<tr>
<th>Drug (cytotoxic)</th>
<th>R-CHOP/ICE</th>
<th>ACVBP + Consolidation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DI (mg/m²/ wk)</td>
<td>Total mg/m²</td>
</tr>
<tr>
<td>Rituximab</td>
<td>187.5</td>
<td>1500</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>25</td>
<td>200</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>500</td>
<td>4000</td>
</tr>
<tr>
<td>Vincristine</td>
<td>0.7</td>
<td>5.6</td>
</tr>
<tr>
<td>Prednisone</td>
<td><em>250</em></td>
<td><em>2000</em></td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>2500</td>
<td>15000</td>
</tr>
<tr>
<td>Etoposide</td>
<td>150</td>
<td>900</td>
</tr>
<tr>
<td>Carboplatin</td>
<td><strong>2.5</strong></td>
<td><strong>45</strong></td>
</tr>
<tr>
<td>Cytarabine</td>
<td>400</td>
<td>800</td>
</tr>
</tbody>
</table>


---

**New Agents in DLBCL**
Lenalidomide for DLBCL: Impact of Cell of Origin

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>GCB</th>
<th>Non-GCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenalidomide cycles</td>
<td>2 (1-35) 2 (1-35) 4 (1-35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>5 (15-40) 5 (4-3) 4 (4-9-4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>5 (12-3) 5 (4-3) 4 (4-3-5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>7 (4-6) 7 (3-4) 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>14 (8-21) 7 (1-21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0-3) 0 (0-3)</td>
<td>6 (6-9)</td>
<td></td>
</tr>
<tr>
<td>ORR (CR + PR)</td>
<td>11 (2-75) 2 (2-7) 5 (5-9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS, mo</td>
<td>3.6 (1.7) 5.6 (2.2) 2.9 (1.6)</td>
<td>9.6 (2.9)</td>
<td>6.2 (1.6)</td>
</tr>
</tbody>
</table>

Hernandez-ilizaliturri et al, Cancer 2011;117:5058

Frontline RL-CHOP in DLBCL or FL: Phase II Study Design

- Two trials with slightly different dose schedules of lenalidomide
- Compared with historical R-CHOP control (with similar baseline characteristics)

Chiappella et al. ASH 2012;Abstract 903; Nowakowski et al. ASH 2012;Abstract 689.
Lenalidomide + R-CHOP21 for Untreated DLBCL in Older Patients: Efficacy

<table>
<thead>
<tr>
<th>Response</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>45 (92)</td>
</tr>
<tr>
<td>CR</td>
<td>42 (86)</td>
</tr>
<tr>
<td>PR</td>
<td>3 (6)</td>
</tr>
<tr>
<td>SD</td>
<td>0</td>
</tr>
<tr>
<td>PD</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>

Chiappella et al. ASH 2012; Abstract 903.

RL-CHOP vs R-CHOP Control Patients Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RaCHOP (N=64)</th>
<th>RCHOP (N=87)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Median (range)</td>
<td>65 (22-87)</td>
<td>61 (41-86)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.53</td>
</tr>
<tr>
<td>Male</td>
<td>40 (62.5%)</td>
<td>50 (57.5%)</td>
<td></td>
</tr>
<tr>
<td>IPI</td>
<td></td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Low</td>
<td>7 (10.9%)</td>
<td>18 (20.7%)</td>
<td></td>
</tr>
<tr>
<td>Low-Intermed.</td>
<td>24 (37.5%)</td>
<td>16 (18.4%)</td>
<td></td>
</tr>
<tr>
<td>High-Intermed.</td>
<td>24 (37.5%)</td>
<td>38 (43.7%)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>9 (14.1%)</td>
<td>15 (17.2%)</td>
<td></td>
</tr>
<tr>
<td>Ann Arbor Stage</td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>2</td>
<td>7 (10.9%)</td>
<td>20 (23.0%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>19 (29.7%)</td>
<td>14 (16.1%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>38 (59.4%)</td>
<td>53 (60.9%)</td>
<td></td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
<td>0.36</td>
</tr>
<tr>
<td>0</td>
<td>30 (46.9%)</td>
<td>32 (36.8%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>28 (43.8%)</td>
<td>41 (47.1%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6 (9.4%)</td>
<td>11 (12.6%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0 (0.0%)</td>
<td>3 (3.4%)</td>
<td></td>
</tr>
</tbody>
</table>

- 87 DLBCL consecutive contemporary patients treated with RCHOP
- Identified in MCR lymphoma database
- Same eligibility: stage 2-4 disease
- No major differences in clinical characteristics

Nowakowski et al. ASH 2012; ASCO 2014

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Outcomes for RL-CHOP v R-CHOP: Case Match Control by Cell of Origin

Non-GC DLBCL

GC DLBCL

Nowakowski et al. ASH 2012; ASCO 2014

E1412: RL-CHOP vs. R-CHOP

N=100 evaluable patients

R-CHOP

N=100 evaluable patients

RL-CHOP

Stratification
• Age
• IPI

10% path ineligibility rate
total ~220 patients

# up to 300 patients can be enrolled to meet a goal of 50
ABC DLBCL patients per arm as defined by GEP

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ROBUST (NCT02285062): Lenalidomide Plus R-CHOP Chemotherapy (R2-CHOP) Versus Placebo Plus R-CHOP Chemotherapy in Patients With Untreated ABC-DLBCL, Phase 3, double-blind, placebo-controlled

**Inclusion**
- DLBCL, ABC-type, untreated
- COD by Lymph2Cx
- Measurable disease by CT/MRI
- ECOG 0-2
- Age 18-80
- IPI > 2

**Exclusion**
- Lymphoma other than DLBCL
- HIV, HBV, HCV active infections
- LVEF < 45%
- Peripheral neuropathy, grade ≥ 2
- Other malignancies < 3 years disease free

**Sample Size/Statistical Plan**
- Sample size: 560
- 90% to detect increase in PFS of 60%

**Evaluation**
- Interim evaluation after cycle 4
- EOT (6 cycles) FDG-PET

**Clinical Endpoints**
- Primary: Progression-free survival
- Secondary: OS, CRR, Duration of CR, TTNT, ORR, QOL

REMARC (NCT01122472): Lenalidomide Maintenance Versus Placebo in Responding Elderly Patients With DLBCL and Treated With R-CHOP in First Line, Phase 3, double-blind, placebo-controlled

**Inclusion**
- DLBCL treated with R-CHOP
- PR or CR
- ECOG 0-2
- Age 60-80
- IPI ≥ 1
- Stage II-IV

**Exclusion**
- Lymphoma other than DLBCL
- Prior indolent lymphoma
- MI within 3 months, unstable CAD; CHF III/IV
- Active HIV, HBV, HBC
- Other malignancies < 3 years disease free

**Sample Size/Statistical Plan**
- Sample size: 650
- ACCRUAL COMPLETE

**Clinical Endpoints**
- Primary: Progression-free survival
- Secondary: Conversion PR to CR, efficacy by R-CHOP response, OS, safety

**Stratifications**
- PR v CR
- Cycles 6 v 8
- Treatment interval 14 v 21
R-CHOP + Bortezomib DLBCL: PFS and OS by Subtype (n = 40)

- Treatment: Bortezomib 0.7 to 1.3 mg/m² on Day 1 and 4 of each R-CHOP-21 cycle
- Patient characteristics (n = 40):

**A3**
Progression Free Survival by Subtypes

**B3**
Overall Survival by Subtypes


PYRAMID (NCT00931918): Randomized phase 2 open-label study of R-CHOP ± bortezomib in patients with untreated non-germinal center diffuse large B-cell lymphoma

Randomization

Arm A: R-CHOP-21 x 6 (n=95)

Arm B: Bortezomib 1.3 mg/m² d1,3 + R-CHOP-21 x 6 (n=95)

Study Start Date: October 2009
EOT Evaluation: IWG 2007 with PET
Last patient in: July 2013

Inclusion
DLBCL, non-GC, untreated (Hans)
Measurable disease
R-IPI ≥ 1
ECOG 0-2

Evaluation
Interim evaluation after cycle 2 CT and FDG-PET
EOT (6 cycles) CT and FDG-PET
Study scans every 3 months

Clinical Endpoints
Primary: Progression-free survival
Secondary: OS, DRR, CRR, Safety

Sample Size/Statistical Plan
Sample size: 190
Success: Increase 2-y PFS from 61% to 75% (68 PFS events)

Leonard et al. ASH 2015; Abstract 811
PYRAMID (R-CHOP ± Bortezomib): Outcomes

Leonard et al. ASH 2015; Abstract 811

Patients at risk:
R-CHOP VR-CHOP PFS probability

<table>
<thead>
<tr>
<th>Time to event (months)</th>
<th>0.0</th>
<th>0.1</th>
<th>0.2</th>
<th>0.3</th>
<th>0.4</th>
<th>0.5</th>
<th>0.6</th>
<th>0.7</th>
<th>0.8</th>
<th>0.9</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-CHOP VR-CHOP</td>
<td>91</td>
<td>92</td>
<td>72</td>
<td>66</td>
<td>60</td>
<td>54</td>
<td>49</td>
<td>44</td>
<td>39</td>
<td>34</td>
<td>29</td>
</tr>
</tbody>
</table>

Treatment group: Censored observations:
R-CHOP VR-CHOP

R-CHOP (N=91)
25%

VR-CHOP (N=92)
18%

2-year PFS: R-CHOP 78%
VR-CHOP 82%

HR (95% CI): 0.73 (0.43, 1.24); p=0.611

Overall Survival

Leonard et al. ASH 2015; Abstract B13

Ibrutinib in Rel/Ref DLBCL: Phase II

Eligibility (N = 70)
- Relapsed/refractory de novo DLBCL
- Progressive disease (PD) after ASCT or ineligible for ASCT
- Archival tissue for central review
- No primary mediastinal DLBCL, transformed DLBCL or CNS involvement

Ibrutinib: 560 mg/d, PO

Wilson WH et al. ASH 2012; Abstract 686.
Younes et al. ASH 2013;Abstract 852

**R-CHOP + Ibrutinib: Phase 1b**

**Schema**

- **PART 1:** Newly diagnosed: FL, MCL, DLBCL
  - R-CHOP × 6 cycles maximum; ibrutinib dosed from daily starting day 3
- **PART 2:** DLBCL only
  - R-CHOP + Ibrutinib
  - 3 dosing cohorts: 280 mg, 420 mg, 560 mg

- **Dose reductions:**
  - 4 patients required dose reduction of ibrutinib
    - Febrile neutropenia (FN) G3 (N=2)
    - Diarrhea G3 (N=1)
    - Prolonged bleed time (N=1)
  - 2 patients required dose reduction of doxorubicin due to FN
  - 7 patients required dose reduction of vincristine with the majority in cycle 4/5

- **Efficacy (N=22):**
  - ORR 100%: CR 91%, PR 9%
  - Non-GC DLBCL: CR 4/4
  - GC DLBCL: CR 12/14, PCR 2/14
  - Not assigned: CR 4/4

---

**PHEONIX (NCT01855750): Ibrutinib in Combination With R-CHOP in Subjects With Newly Diagnosed Non-Germinat Center Diffuse Large B-Cell Lymphoma, Phase 3, double-blind, placebo-controlled**

**Inclusion**
- DLBCL, non-GC, untreated
- Stage II (not candidates for RT), III, IV
- ≥1 measurable site
- R-IPI ≥ 1
- ECOG 0-2
- LVEF WNL

**Exclusion**
- Major surgery within 4 weeks
- CNS disease
- Prior indolent lymphoma
- Warfarin
- Concomitant CYP3A inhibitors

**Sample Size/Statistical Plan**
- Sample size: 800
- Study completion: 50% deaths or 7 years

**Evaluation**
- Interim evaluation after cycle 4
- EOT (6-8 cycles) PDG-PET

**Stratifications**
- R-IPI ≥ 1.5
- US v Rest of World
- 6 v 8 cycles

**Clinical Endpoints**
- Primary: Event-free survival
- Secondary: PFS, OS, CR, QOL, ibrutinib: clearance, volume of distribution, AUC, minimal concentration, AEs
Lymphoma Disease Management Team

Lymphoma Service
John Gerecitano
Paul Hamlin
Steve Horwitz
Andrew Inleikofer
Anita Kumar
Matt Matasar
Alison Moskowitz
Craig Moskowitz
Ariela Noy
Lia Palomba
Carol Portlock
Jonathan Schatz
David Strauss
Anas Younes, Chief
Andrew Zelenetz

Nuclear Medicine
Heiko Schoder
Neetha Pandit-Tasker
Jorge Carasquillo
Radiology
James Caravelli
Jurgen Rademaker

Radiation Oncology
Joachim Yahalom

Lymphoma Transplant Program
Matt Matasar
Craig Sauter
Craig Moskowitz
Juliet Barker
Jenna Goldberg
Miguel Perales
Sergio Giralt
Hematopathology
Ahmet Dogan
Maria Arcila
April Chiu
Oscar Lin
Chris Park
David Park
Filiz Sen

NCCN Member Institutions

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